REMARKS

A. Status of the Claims

Claims 1-18 were examined and remain pending. New claim 35 is added. Claims 3 and 12 have been amended to address the indefiniteness rejection of claim 3, and for no other reason. Claim 4 has been amended to clarify the scope of the claim.

B. The Claims Are Enabled

The Office rejects claims 1-18 under 35 U.S.C. § 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention[.]" October 2004 Office Action at p. 2. Applicants respectfully traverse.

The claims of this application are, in essence, concerned with mathematics, which is a well-established art. *See* Second Declaration of Rama Ranganathan ("Second Decl.") at ¶ 12 (enclosed). Thus, the art to which the claimed subject matter pertains is predictable, and the level of skill in it is high. *Id.* at 12-14. In light of these and the other *Wand* factors discussed below, the claims are enabled, and the rejection should be withdrawn.

Claim 1 is directed to a method of identifying one or more positions in a polymer family. The method includes:

(a) accessing data representing a multiple sequence alignment (MSA) of a plurality of polymer sequences; and

(b) identifying one or more evolutionarily conserved amino acid positions within the MSA using the following equation:

$$\Delta G_i^{stat} = kT^{*}\sqrt{\sum_x\left(\ln\frac{P_i^x}{P_{MSA}^x}\right)^2}$$

wherein:

i is a position in the MSA;

ΔG_i^{stat} is the conservation energy value for position i;

P_i^x is the probability of monomer x at position i;

P_{MSA}^x is the probability of monomer x in the MSA; and

kT* is an energy unit, where k is Boltzmann's constant.

Claim 10 is directed to a method of identifying one or more positions in a polymer family, the method comprising:

(a) accessing data representing a multiple sequence alignment (MSA) of a plurality of polymer sequences;

(b) calculating a conservation energy value for each position in the MSA using the following equation:

$$\Delta G_i^{stat} = kT^* \sqrt{\sum_x \left(\ln \frac{P_i^x}{P_{MSA}^x} \right)^2}$$

wherein:

i is a position in the MSA;

ΔG_i^{stat} is the conservation energy value for position i;

P_i^x is the probability of monomer x at position i;

P_{MSA}^x is the probability of monomer x in the MSA;

kT* is an energy unit, where k is Boltzmann's constant; and

(c) identifying one or more positions within the MSA that have statistically significant conservation energy values.

A review of the following *Wand* factors show why these claims are enabled.

a. The breadth of the claims

The recitation in claim 1 and claim 10 of "accessing data representing a multiple sequence alignment (MSA) of a plurality of polymer sequences" pertains to data that exists (*e.g.*, now or at some point in the future). Second Decl. at ¶ 6. Furthermore, claim 1's recitation of "identifying one or more evolutionarily conserved amino acid positions within the MSA" using

the claimed equation, which specifies parameters that are defined in the claim, can **necessarily be performed** if the claimed parameters are known or determined (*e.g.*, through calculation) and the MSA concerns a polymer that has one or more amino acid positions. Thus, if P_i^x and P_{MSA}^x are known or determined, and the MSA concerns a polymer that includes one or more amino acid positions, the claimed identification can necessarily be achieved when the claimed equation is used. Second Decl. at ¶ 10. P_i^x and P_{MSA}^x can both be calculated using Equation 2 on page 18 of the specification. *Id.* at ¶ 9.

Furthermore, claim 10's recitation of "calculating a conservation energy value for each position in the MSA" using the recited equation, and its recitation of "identifying one or more positions within the MSA that have statistically significant conservation energy values" can **necessarily be performed** if the claimed parameters are known or determined (*e.g.*, through calculation). Thus, if P_i^x and P_{MSA}^x are known or determined (*e.g.*, using Equation 2 on page 18), the claimed identification can necessarily be achieved if the claimed equation is used. *Id.* at ¶ 11.

b. The nature of the invention

Claim 1 is directed to the use of an equation to identify one or more evolutionarily conserved amino acid positions within an MSA of a plurality of polymer sequences. Claim 10 is directed to calculating a conservation energy value for each position an MSA of a plurality of polymer sequences using an equation, and identifying one or more positioning within the MSA that have statistically significant conservation energy values.

c. The state of the prior art

No prior art teaches or suggests the identification of one or more evolutionarily conserved amino acid positions within an MSA of a plurality of polymer sequences using the

claimed equation. No prior art teaches or suggests calculating a conservation energy value for each position an MSA of a plurality of polymer sequences using an equation, and identifying one or more positioning within the MSA that have statistically significant conservation energy values.

d. The level of one of ordinary skill in the art

The art to which this invention pertains is bioinformatics that involves the use of an equation based on known/calculatable parameters. Second Decl. at ¶ 12. The level of skill in this art is high because individuals working or researching in the bioinformatics field generally possess a masters or doctorate degree. *Id.* at ¶ 13.

e. The level of predictability in the art

The predictability of this art is high. Second Decl. at ¶ 14. Claims 1 and 10 each recite the use of an equation that is based on parameters that are known or that can be determined (e.g., by calculation). With those parameters, a user can necessarily achieve the claimed identifications if the claimed equation is used. *Id.* at ¶¶ 10-11. In essence, claims 1 and 10 concern mathematics, which is a well-established art. *Id.* at ¶ 12.

To illustrate the predictability of this art and the applicability of the methods of claims 1 and 10 to MSAs of polymers other than those from the PDZ domain family, Dr. Ranganathan a method that could be used to fulfill the steps of claim 1 (if one or more evolutionarily conserved amino acid positions are identified) or claim 10 (if a conservation energy value for each position in the MSA is calculated, and one or more positions with statistically significant conservation energy values are identified) to an arbitrary model MSA of a made-up polymer. *Id.* at ¶ 15. The polymer was a twelve-residue polymer made up of 5 different types of monomers. *Id.* at ¶ 16.

He assumed that the mean frequencies of the monomers in the universe of all known such polymers was known. Second Decl. at ¶ 16.

Using a computer, he generated the frequencies of the five monomers in each position in a 100-sequence MSA that he assumed to exist. Second Decl. at ¶¶ 17. He provided these frequencies and the overall frequency of each monomer in the MSA in a table in paragraph 17 of his Second Declaration. He converted the frequencies at at least one MSA position (and, in this case, at each MSA position) and in the MSA overall into binomial probabilities to arrive at values for P_i^x and P_{MSA}^x, respectively, using Equation 2 on page 18 of the application, given the mean frequency of that MSA position (and, in this case, each MSA position) in all known polymers (which he assumed). *Id.* at ¶ 18.

Finally, he calculated the conservation energy value (ΔG_i^{stat}) for at least one position i (and, in this case, each position i) in the MSA from the binomial probabilities using the equation recited in claim 1. *Id.* at ¶ 19. The plot provided in paragraph 19 of the Second Declaration reveals that some positions show conservation energy values close to zero and others show conservation energy values that differ to a greater degree from zero. These values quantitatively capture the degree of conservation of at least one site (and, in this case, each site) in the MSA. *Id.*

As the results of the mock experiment show, the claimed equation may be used to achieve the claimed identification of claims 1 and 10 provided the equation's parameters are known/determined. For claim 10, this is true regardless of the type of polymer involved. Second *Id* at ¶ 14. For claim 1, this is true regardless of the type of polymer involved, provided it contains one or more amino acid positions. *Id.*

f. The amount of direction provided by the inventors

Applicants' specification provides the direction needed to calculate the probability parameters recited in claims 1 and 10. Second Decl. at ¶ 9 (explaining that Equation 2 on page 18 can be used to calculate P_i^x and P_{MSA}^x). Applicants have provided an example that shows that the currently claimed algorithm was successfully applied to an MSA of the PDZ protein family to identify one or more evolutionarily conserved amino acid positions. *See* specification at pages 25 and 26. Furthermore, Applicants provide source code (pages 50-53; *see also* page 23, lines 5-6) that can be used to perform at least one embodiment of each of the claimed methods.[1]

g. The existence of working examples

Applicants have provided a working example of how the methods of claims 1 and 10 may be performed to identify one or more evolutionarily-conserved amino acid positions in an MSA. *See* specification at pages 25 and 26. The working example bears a reasonable correlation to the full scope of the claims because the art to which the claimed invention pertains concerns mathematics and is predictable. Second Decl. at ¶¶ 12, 14. If the claimed parameters are known/determinable, the methods of claims 1 and 10 can necessarily be performed to achieve the claimed identification. *Id.* at ¶¶ 10-11.

[1] The Office's statement that the source codes "is not persuasive in that the claims do not contain limitations of source code" is legally flawed. There is no requirement in patent law that, in a predictable art such as the one to which the claimed invention pertains, claim 1 must be drafted so as to be limited precisely to a particular embodiment disclosed in the specification. Claim 1 would be superfluous to the specification were that the case. The source code **is relevant** to the enablement question because it is evidence of one embodiment that can be used to perform the claimed method.

h. The quantity of experimentation needed

The quantity of experimentation necessary to perform the claimed methods on an MSA other than the one disclosed in the specification pertaining to the PDZ domain family is minimal. This follows because the claims assumes the MSA exists, and the probability parameters specified in the claims can be determined as set forth in the specification. Second Decl. at ¶ 9.

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Taking the *Wand* factors into account, it is clear that Applicants have enabled the full scope of claims 1-18. Accordingly, the enablement rejection of these claims should be withdrawn.

Applicants now address some of the Office's statements/questions:

- Chemical polymers (*e.g.*, unstructured peptides) exist that have one or more amino acids but do not include protein. Second Decl. at ¶ 20. Thus, the Office's statement that "identifying one or more evolutionarily conserved amino acid positions in a chemical polymer is nonsense if the chemical polymer does not include protein" is factually incorrect.

- The Office states that "the specification is devoid of any information showing an alignment of chemical or other polymers and how these types of polymers would be used in said invention." October 2004 Action at page 3. This statement is factually and legally incorrect. Applicants are not obligated to identify all the different MSAs to which the claimed invention could be applied. The Office has already admitted that "MSA techniques are **well known** in the art and that Applicant is **not** claiming a method to perform an MSA." *Id.* Furthermore, the probability parameters specified in the claim are polymer-generic. Thus, no more information is needed to show how the claimed invention can be applied to an MSA of a polymer other than, for example, one in the PDZ domain family provided an MSA for the polymer exists (which could, of course, be created using known techniques) and provided (in the case of claim 1) the polymer includes one or more amino acid positions.

- The Office states that the specification "**is silent as to other polymers** amenable to the method." October 2004 Action at page 3. This is factually incorrect. On page 29, line 29 – page 30, line 2, the specification states, "Any polymer of monomers may be analyzed with the inventive methods. Application of the

inventive methods is not limited to biological sequences, as it may be applied to chemical polymers, drugs and other compounds."

- The Office asks, "Are polyacrylamide polymers able to be used in this method? How would such non-protein polymers be aligned? Could free energy calculations be performed?" October 2004 Action at page 3. Claim 1 concerns polymers that have one or more amino acids. However, claim 10 is not amino acid-specific. Such polymers could be aligned using known techniques. As Applicants have stated before, the claims relate to accessing data representing an MSA; they do not recite the creation of an MSA.

- The Office states that the specification "is completely devoid of information as to how any other type of polymer [other than protein sequences] is to be selected and aligned." October 2004 Action at pages 3-4. This statement is inconsistent with the Office's admission that "MSA techniques are **well known** in the art and that Applicant is **not** claiming a method to perform an MSA." *Id.* at page 3. Again, Applicants are not claiming the creation of an MSA; Applicants are claiming accessing data representing an MSA. The claim language assumes an MSA exists.

B. Claim 3 Is Definite

Claim 3 has been amended to address the Office's indefiniteness rejection. Claim 12 has been amended in the same fashion. Both claims are definite, and Applicants request that the indefiniteness rejection of claim 3 be withdrawn.

C. New Claim 35 Is Enabled

New claim 35 is enabled for substantially the reasons provided above with respect to claims 1 and 10.

D. Petition for Extension of Time in This and Future Responses

Applicants petition for a 3-month extension of time in which to respond to the October 20, 2004 Office Action. A check covering the process fee for the requested extension is enclosed. If the check has been inadvertently omitted, or if any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason relating to the enclosed materials, or should an overpayment be included, the Office is authorized to deduct or credit the appropriate fees from or to Fulbright & Jaworski Deposit Account No.: 50-1212/UTSD:645US.

The Office is further authorized to treat any concurrent or future reply that requires a petition for an extension of time under 37 C.F.R. § 1.136(a) to be timely as incorporating a petition for an extension of time for the appropriate length of time, and to deduct all required fees under 37 C.F.R. §§ 1.16 to 1.21 relating to any such replies of other relevant papers from Fulbright & Jaworski Deposit Account No.: 50-1212/UTSD:645US.

E. Conclusion

Claims 1-18 are in condition for allowance. Should Examiner Clow have any questions, comments, or suggestions relating to this application, she is invited to contact Applicants' attorney at (512) 536-3031.

Respectfully submitted,

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